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A Randomized Controlled Trial (SUPER)

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Surveillance With PET/CT and Liquid Biopsies of Stage I-III Lung Cancer Patients After Completion of Definitive Therapy: A Randomized Controlled Trial (SUPER)

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Abstract

Despite increased focus on prevention as well as improved treatment possibilities, lung cancer remains among the most frequent and deadliest cancer diagnoses worldwide. Even lung cancer patients treated with curative intent have a high risk of relapse, leading to a dismal prognosis. More knowledge on the efficacy of surveillance with both current and new technologies as well as on the impact on patient treatment, quality of life, and survival are urgently needed. We therefore designed a randomized phase 3 trial. In one arm, every other computed tomography (CT) scan is replaced by positron emission tomography/CT, the other arm is the standard follow-up scheme with CT. The standard arm is identical to the current national Danish follow-up program. The primary endpoint is to compare the number of relapses treatable with curative intent in the 2 arms. We aim to include 750 patients over a 3-year period. Additionally, we will test the feasibility of noninvasive lung cancer diagnostics and surveillance in the form of circulating tumor DNA analysis. For this purpose, blood samples are collected before treatment and at each following control. The blood samples are stored in a biobank for later analysis and will not be used for guiding patient treatment decisions.

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Introduction

The 5-year survival rate of Danish lung cancer patients diagnosed with locoregional disease ranges from 43% for patients with stage I disease, 27% for stage II disease, and 10% for patients with stage III disease.^{1,2} Because of the high risk of relapse, active surveillance after curative-intent treatment is recommended.³ Unfortunately, our knowledge of how to do this most efficiently is poor. Nonetheless, a standardized surveillance program for patients treated for lung cancer was introduced in Denmark in 2016.⁴ For patients with stage I-III lung cancer, this program includes clinical control and contrast-enhanced (ce) computed tomography (CT) every 3 months for the first 2 years after definitive treatment, then every 6 months from year 3 to 5.

The SUPER Trial: Study Protocol

Objectives

To improve early detection of treatable relapse of lung cancer, thereby improving patient survival and quality of life (QoL).

Design

The study is an investigator-initiated national multicenter randomized clinical trial designed first to assess if surveillance with

¹⁸F-fludeoxyglucose positron emission tomography (PET)/ceCT can increase the number of treatable relapses, and second to concurrently collect liquid biopsy samples for later analysis, potentially enabling even earlier and minimally invasive detection and characterization of relapse.

The aim is to include and randomize a total of 750 patients from all 5 regions of Denmark from the departments of pulmonology and oncology with stage I-III non-small-cell lung cancer (NSCLC) after treatment with curative intent. These patients are currently, after their definitive treatment, followed with ceCT (thorax and upper abdomen) every 3 months for the first 2 years. In the trial, patients will be randomized 1:1 to the interventional arm (arm A) with PET/ceCT (vertex to the midfemoral region) replacing ceCT at months 6, 12, 18, and 24, or to the standard arm (arm B) with ceCT every 3 months. In both arms, patients will undergo clinical evaluation, QoL assessment, and liquid biopsy sampling every 3 months. Patients will be stratified by site, sex, and lung cancer stage.

The primary endpoint is number of relapses treatable with curative intent. Secondary endpoints are as follows: time to verified relapse, overall survival (OS), OS for patients with relapse, performance status at relapse, QoL at relapse, number and type of invasive procedures to assess whether patients experienced relapse, number

Figure 1 Patient Flow

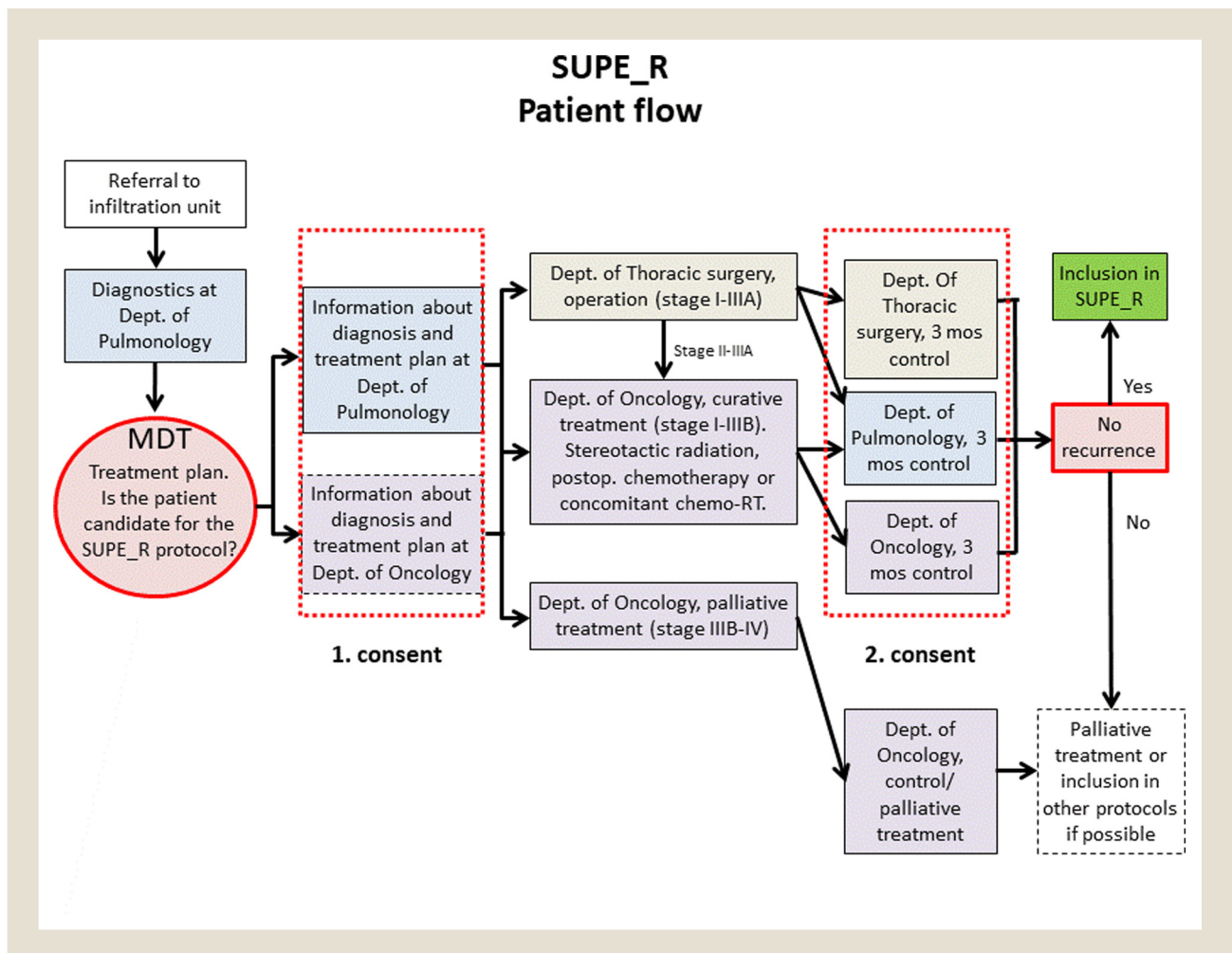
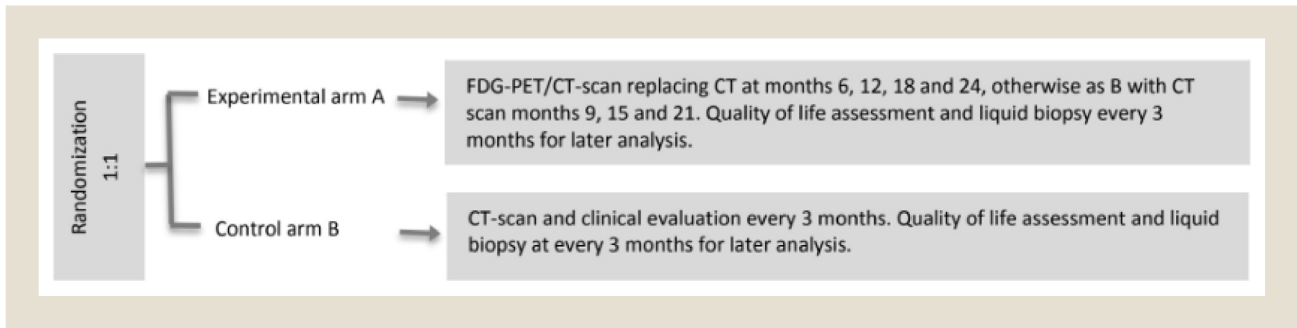


Figure 2 Randomization Arms



and type of invasive procedures to assess incidental findings, including any adverse events due to these invasive procedures, cost-effectiveness and health care costs, and type of treatment after verification of relapse.

A study scheme is shown in Figure 1, and the 2 randomization arms are shown in Figure 2.

Eligibility

Patients are eligible if they are diagnosed with stage I-III lung cancer treated with curative intent with one or more of the following modalities: resection, chemotherapy, radiofrequency ablation, and radiotherapy, with or without adjuvant treatment. Also, the patients shall have no evidence of recurrent disease on the control ceCT performed 3 months after definitive treatment.

Follow-up

After 24 months of follow-up, all included patients will continue in the standard follow-up program for years 3 to 5.

For primary endpoint analysis, patients will be followed until the first confirmed relapse or for up to 3 years after randomization, whichever comes first. For survival analysis, patients will be followed until death or for a minimum of 1 year after the last scan performed related to this project. Because it may be difficult to discriminate if a relapse is a true relapse of the lung cancer or a new primary lung cancer, a relapse will comprise both. If a secondary cancer is diagnosed during the project period, patient data will be censored at this point, unless it is a cancer with a prognosis expected to be significantly better than NSCLC, such as small localized tumors in the breast, thyroid, or colon. All findings that hint at relapse and/or secondary cancer will, as far as clinically possible, be verified by biopsy. Diagnosis and treatment of relapse will ultimately be decided by the local multidisciplinary tumor board.

Biomarker and QoL Analyses

Liquid biopsy samples will be drawn before initiation of therapy (baseline) and at follow-up visits as close to the scheduled imaging (ceCT or PET/ceCT) as possible. All samples will be analyzed for amount of cell-free DNA and for selected tumor markers in circulating tumor DNA (ctDNA). The dynamics of ctDNA will be compared to ceCT or PET/ceCT findings. In addition, if feasible, potential biomarkers related to disease relapse will be assessed.

To examine the participants' QoL during follow-up and at the time of relapse, they will be asked to fill in a QoL questionnaire (European Organization for Research and Treatment of Cancer

QLQ C-30, LC-13, and GAD-7). The purpose of this is 2-fold: first, to explore how the intervention and detection of relapse influences patient-experienced QoL, and second, to enable a cost-effectiveness analysis that examines the cost per quality-adjusted life-year (QALY), an outcome measure combining quantity and QoL after a given intervention.

Statistical Analysis

The protocol started inclusion in the Capital region in October 2018. Two more regions started inclusion in January 2019 and yet another one in October 2019. The remaining region will soon follow.

To detect a 15% increase in the proportion of patients with relapses offered treatment with curative intent (from the currently estimated 31%² to 46%) in the PET arm, power calculations resulted in a sample size of 330 patients, 165 patients per group. Estimating that 45% of the included patients will experience relapse within 24 months, a total of $165/0.45 = 367$ patients should be included in each arm (for a total of 734). We aim to include 375 patients in each arm. The Fisher exact test will be used to test for an increase in the proportion of patients with relapse.

The cost-effectiveness of the 2 arms is assessed with the incremental cost-effectiveness ratio—that is, the ratio of net health care costs to net QALYs.

Analysis of covariance will be used to assess the difference in changes in QoL score (symptom burden and functional scales) and performance status between the 2 arms, adjusting for QoL score at baseline. Median OS will be estimated via the Kaplan-Meier method.

Ethics

The study will be performed in accordance with the Declaration of Helsinki and Danish law. All patients must provide written informed consent before inclusion in the study, and all data will be treated with confidentiality. Approval by the Regional Committee on Health Research Ethics and the Danish Data Protection Agency was obtained before study initiation (approval H-18009536). Patient information is protected by the Personal Data and Health Acts Act. The study is registered at [ClinicalTrials.gov](https://www.clinicaltrials.gov) (NCT03740126).

Discussion

In recent guidelines, PET/ceCT has replaced ceCT as the primary staging examination.⁵ The superiority of PET/CT is primarily based on an increased sensitivity for mediastinal and distant

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metastases.^{6,7} Currently, PET/CT is neither routinely performed nor recommended during follow-up, except in cases of suspected relapse in patients who are candidates for salvage therapy or after inconclusive ceCT.⁸ Especially after radiotherapy, ceCT is known to have limited accuracy, which can potentially delay the diagnosis of a relapse.⁹ The diagnostic accuracy of PET/ceCT for detection of relapse has been evaluated in several mainly small and retrospective, highly heterogeneous studies. These were presented in a comprehensive review including 13 studies with 1035 patients in total. This review emphasizes the superior accuracy of PET/ceCT over ceCT, mainly because of its improved sensitivity.¹⁰

A Swiss single-center randomized study of 93 patients compared PET/ceCT with ceCT of the chest as surveillance after curatively treated NSCLC. Scans were performed every 6 months. The study did not find PET/ceCT to be better than ceCT in detection of recurrence, however, thus emphasizing that the sample size was too small to detect minor differences or to discriminate between treatment modality and stage.¹¹ Despite the scarcity of evidence, the use of PET/ceCT for follow-up has been increasing, but better evidence for the role of PET/ceCT is needed.¹²

Blood carries various potential cancer biomarkers, such as circulating tumor cells, microRNA, and ctDNA. In particular, ctDNA detected in plasma or serum has been shown to be a valuable prognostic and predictive marker for early detection of relapse.^{13,14} It is now possible to detect ctDNA in patients with low tumor burden (eg, in early-stage NSCLC or early in the course of relapse).^{13,15} To our knowledge, this is the first nationwide initiative that can potentially deliver biostatistically significant evidence for implementation of liquid biopsy and ctDNA analysis in standard patient care.

Conclusion

This trial combining collection of data regarding imaging, QoL, liquid biopsy, and cost in a multicenter randomized clinical setting will provide the scientific basis for improving surveillance and treatment of patients with lung cancer as well as provide knowledge transferable to other groups of cancer patients.

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Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Engholm GFJ, Christensen N, Kejs AMT, et al. NORDCAN: cancer incidence, mortality, prevalence and survival in the Nordic countries, version 7.0. Association of the Nordic Cancer Registries; Danish Cancer Society. Available at <http://www.ancr.nu/>. Accessed: December 17, 2014.
2. Dansk LungeCancerGruppe. Erfaringer med opfølgning af fynske patienter efter kurativt interenderet behandling af første tilfælde af lungecancer fundet ved udredning i perioden 2007-2013. Opgjort November 2014. Available at <https://www.lungecancer.dk/wp-content/uploads/2018/09/1.pdf>. Accessed: September 19, 2017.
3. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: lung cancer, version 5.2017. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx.
4. Sundhedsstyrelsen (National Board on Health). Opfølgingsprogram for Lungekræft (Follow-up Program for Lung Cancer). Available at: <https://www.sst.dk/da/nyheder/2016/opfoelgningsprogram-for-lungekraeft>. Accessed: June 1, 2016.
5. De Leyn P, Doooms C, Kuzdzal J, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. *Eur J Cardiothorac Surg* 2014; 45:787-98.
6. Fischer B, Lassen U, Mortensen J, et al. Preoperative staging of lung cancer with combined PET-CT. *N Engl J Med* 2009; 361:32-9.
7. Madsen PH, Holdgaard PC, Christensen JB, Hoiland-Carlsen PF. Clinical utility of F-18 FDG PET-CT in the initial evaluation of lung cancer. *Eur J Nucl Med Mol Imaging* 2016; 43:2084-97.
8. Sheikhbahaei S, Mena E, Yanamadala A, et al. The value of FDG PET/CT in treatment response assessment, follow-up, and surveillance of lung cancer. *AJR Am J Roentgenol* 2017; 208:420-33.
9. Jimenez-Bonilla JF, Quirce R, Martinez-Rodriguez I, et al. Diagnosis of recurrence and assessment of post-recurrence survival in patients with extracranial non-small cell lung cancer evaluated by ¹⁸F-FDG PET/CT. *Lung Cancer* 2013; 81:71-6.
10. He YQ, Gong HL, Deng YF, Li WM. Diagnostic efficacy of PET and PET/CT for recurrent lung cancer: a meta-analysis. *Acta Radiol* 2014; 55:309-17.
11. Gambazzi F, Frey LD, Bruehlmeier M, et al. Comparing two imaging methods for follow-up of lung cancer treatment: a randomized pilot study. *Ann Thorac Surg* 2019; 107:430-5.
12. Sharma G, Nishi SP, Lin YL, Kuo YF, Goodwin JS, Riall TS. Pattern of imaging after lung cancer resection, 1992-2005. *Ann Am Thorac Soc* 2016; 13: 1559-67.
13. Bortolin MT, Tedeschi R, Bidoli E, et al. Cell-free DNA as a prognostic marker in stage I non-small-cell lung cancer patients undergoing stereotactic body radiotherapy. *Biomarkers* 2015; 20:422-8.
14. Kotsakis A, Koinis F, Katsarou A, et al. Prognostic value of circulating regulatory T cell subsets in untreated non-small cell lung cancer patients. *Sci Rep* 2016; 6: 39247.
15. Newman AM, Bratman SV, To J, et al. An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage. *Nat Med* 2014; 20: 548-54.